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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,242	04/01/2004	James Freddo	PC25581A	9207

28940 7590 11/03/2006

PFIZER INC
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EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 11/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/816,242	FREDDO ET AL.	
	Examiner	Art Unit	
	Shirley V. Gembeh	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-48* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Office Action mailed 8/23/06 has been vacated in favor of the following action, because the action sent out already examined the method claims, the composition claims are now examined together with the method claims and the restriction is withdrawn.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on July 02, 2004, September 09, 2004 and December 07, 2004 have been received and acknowledged. Examiner notes that the IDS dated December 07, 2004 is missing page 2 of 2.

Response to restriction

Applicants' argument have been considered and the restriction is withdrawn.

Status of Claims

Claims 1-48 are pending in this office action.

Claim Objections

Claim 1 is objected to because of the following informalities: The abbreviation AUC, should be given as its full name or with the full name in parenthesis therewith when first used. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a written description rejection.

A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics,

i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" for the solvate, active metabolite or prodrug, thereof means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]."

In other words, the Applicant has not described with sufficient clarity what these solvates, active metabolites, prodrugs thereof are.

II. Claims 17-28, 30-45 and 47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a written description rejection.

A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product

claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" for the solvate, active metabolite or prodrug, thereof means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the

genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]."

In other words, the Applicant has not described with sufficient clarity what these solvates, active metabolites, prodrugs thereof are.

III. Claims 17-28, 30 and 32-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a representative of abnormal cell growth or cancer, does not reasonably provide enablement for treating a wide variety of abnormal cell growth or cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2nd 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

Nature of the invention

The nature of the invention is methods of treating abnormal cell growth or cancer in a patient, comprising administering the instant compound of formula I and its acceptable solvates, active metabolites, prodrugs, racemates or enatiomers to a patient in need thereof. As stated, however, claims 17-28, 30-45 and 47-48 recite that any or a large representation of variety of abnormal cell growth or cancer is intended.

State of the prior art and the predictability or lack thereof in the art

The state of the prior art is that it involves screening *in vitro* and *in vivo* to determine which compounds of claimed formula I and its' solvates, active metabolites, prodrugs, racemates or enatiomers exhibited the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below.

There is a vast range of forms that abnormal cell growth or cancer can take, causes for the problem, and biochemical pathways that mediate the abnormal cell growth and or cancer reaction. There is no common mechanism by which a large, or even most, abnormal cell growth or cancer arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, leukotrienes, cytokines, and many, many others. Accordingly,

treatments for diseases associated with abnormal cell growth or cancer are normally tailored to the particular type of cancer present. It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue. Further, their mode of action is often unknown or very unpredictable and administration of the drugs can be accompanied by undesirable side effects.

Thus, in the absence of a showing of correlation between some of or a representation of the diseases claimed as capable of being treated by compounds of the instant claims, one of skill in the art is unable to fully predict possible results from the administration of the compounds due to the unpredictability of the role of the various compounds and the disease

Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The quantity of experimentation needed is undue experimentation. One of skill in the art would first need to determine the type of abnormal cell proliferation/growth or cancer to be treated, and then determine which of the large representation of compounds of formula I and its' solvates, active metabolites, prodrugs, racemates or enatiomers would be suitable for said treatment and/or prevention.

Level of ordinary skill in the art

The level of ordinary skill in the art is high. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and/or *in vivo* screening to

determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Hence, the specification fails to provide sufficient support of the broad use of the compounds of the claims for the treatment of any disease. As a result necessitating one of skill in the art to perform an exhaustive search to determine which diseases can be treated by what compounds of the instant claims in order to practice the claimed invention.

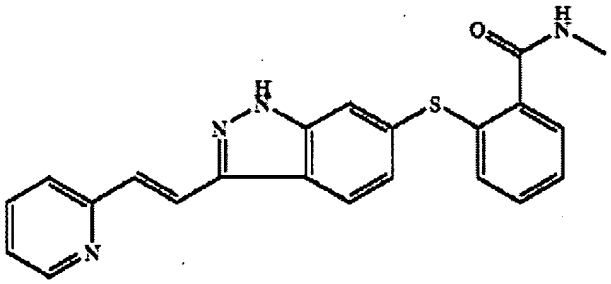
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Kania et al. WO 2001/02369 now a US Patent 6,531,491.

Kania et al. teach the instant claims 1and 8, a composition administering a compound of formula 1 as shown below to a mammal (see col. 16, lines

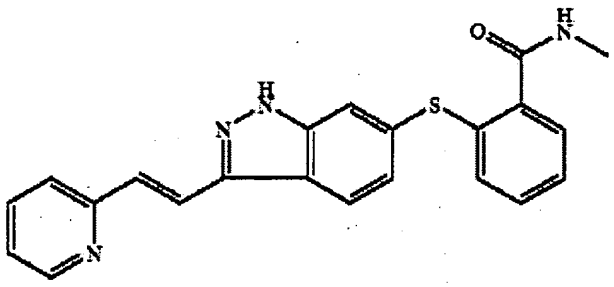


25+) (see col. 11 lines 35+) in a pharmaceutically acceptable salt, solvate (see col. 13, lines 19-30) as in claims 17 and 32 in an amount effective to provide a 24 hour area under the concentration curve (AUC) blood plasma is anticipated because the reference teaches a Cmin of 7hours to have an AUC of no more than 4500 (see table 6, col. 377 and 378 item (32a)). Inother for one to determine the AUC factor of the drug the concentration of the drug must be given, as in claim 8, however, that limitation is missing in the claim, (see table 6 col. 377 and 378, lines 24+), thus making claims 2-5 anticipatory. With regards to claim 8 as long as a given concentration is administered, the AUC will be released into the blood plasma and therefore have a concentration relative to the rate of absorbtion. The reference also teaches administering the compound orally (see col. 21, lines 56) as in claims 6 and 15 in a tablet or capsule as in claims 7 and 16. The dosage preferred in the reference is 0.001-50 mg, thus making claims 8-14 anticipatory (see col. 21, lines 30+).

Claims 17-30 and 32-47 rejected under 35 U.S.C. 102(b) as being anticipated by Kania et al. WO 2001/02369 now a US Patent 6,531,491.

Kania et al. teach methods of treating cancer and other disease states associated with unwanted angiogenesis and/or cellular proliferation (see abstract),

administering a compound of formula 1 as shown below to a mammal (see col. 16,



lines 25+) (see col. 11 lines 35+) in a pharmaceutically acceptable salt, solvate (see col. 13, lines 19-30) as in claims 17 and 32 in an amount effective to provide a 24 hour area under the concentration curve (AUC) blood plasma is anticipated because in other to determine the AUC the concentration of the drug must be given, since that limitation is missing in the claim, (see table 6 col. 377 and 378, lines 24+), thus making claims 18-21 are anticipatory. The reference also teaches administering the compound orally (see col. 21, lines 56) as in claims 22 and 39. The dosage preferred in the reference is 0.001-50 mg, thus making claims 32 in part and 33-38 anticipatory (see col. 21, lines 30+).

With regards to claims 23-27 and 40-44, the reference teaches courses of treatment repeated at appropriate intervals, thus making the claims anticipatory that the actual dosages of the agents and interval administered will vary according to the particular complex being used, the particular composition formulated, the mode of administration and the particular site, host and disease being treated (see col. 21, lines 22+). As to claims 28 and 45 the abnormal cellular proliferation is cancer (see abstract) wherein the cancer is lung cancer (see col. 275, lines 50+) as in claims 29 and 46.

Claim Rejections - 35 USC § 103

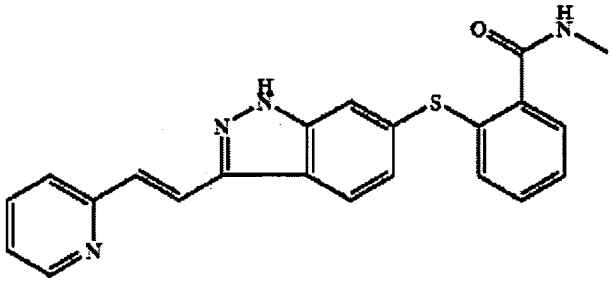
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kania et al. WO 2001/02369 now a US Patent 6,531,491 in view of Sweeney et al. Cancer Res.

Kania et al. teach methods of treating cancer and other disease states associated with unwanted angiogenesis and/or cellular proliferation (see abstract), administering a compound of formula 1 as shown below to a mammal (see col. 16, lines



25+) (see col. 11 lines 35+) in a pharmaceutically acceptable salt, solvate (see col. 13, lines 19-30) as in claims 17 and 32 in an amount effective to provide a 24 hour area under the concentration curve (AUC) blood plasma is anticipated because in other to determine the AUC the concentration of the drug must be given, since that limitation is missing in the claim, (see table 6 col. 377 and 378, lines 24+), thus making claims 18-21 are anticipatory. The reference also teaches administering the compound orally (see col. 21, lines 56) as in claims 22 and 39. The dosage preferred in the reference is 0.001-50 mg, thus making claims 32 in part and 33-38 anticipatory (see col. 21, lines 30+).

With regards to claims 23-27 and 40-44, the reference teaches courses of treatment repeated at appropriate intervals, thus making the claims anticipatory that the actual dosages of the agents and interval administered will vary according to the particular complex being used, the particular composition formulated, the mode of administration and the particular site, host and disease being treated (see col. 21, lines 22+). As to claims 28 and 45 the abnormal cellular proliferation is cancer (see abstract) wherein the cancer is lung cancer (see col. 275, lines 50+) as in claims 29 and 46.

Although the Kania et al. reference did not teach addition or combination of docetaxel to the compound of formula 1 in claims 17 and 32, one of ordinary skill would have used the teachings suggested by Goodman and Gilman and combined the above compound of formula 1 with docetaxel.

Sweeney et al. teach the combination of a vascular endothelial cell growth factor with docetaxel (VEGF).

One of ordinary skill in the art would have been motivated to combine the teachings of Kania et al with that of Sweeney et al, because in the Sweeney et al reference a VEGF compound was used with docetaxel, therefore motivating one of ordinary skill to switch the compound of Sweeney et al. with that of Kania et al. and combine with docetaxel because it is well know in the art of cancer that adjuvant therapy are used to give synergistic effect to the cell proliferation.

Thus, the claimed invention was prima facia obvious to make and use at the time it was made.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shirley V. Gembeh whose telephone number is 571-272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SVG
10/27/06

Ardin H. Marschel 10/29/06
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SUPERVISORY PATENT EXAMINER